Glucose lowering and anti-atherogenic effects of incretin-based therapies: GLP-1 analogues and DPP-4-inhibitors

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Abstract: BACKGROUND: Type 2 diabetes is a chronic, progressive disease with a multi-faceted pathophysiology. Beyond the known defects of insulin resistance and beta-cell insufficiency, derangement of incretin hormones normally produced from the gut wall in response to food intake play an important role. In recent years, the 'incretin-based' therapies (IBTs) have been developed to address hyperglycemia through either mimicking the action of the endogenous incretin glucagon-like polypeptide (GLP-1) (GLP-1 receptor agonists) or by inhibiting the activity of the enzyme that degrades GLP-1 (the dipeptyl peptidase-4 inhibitors). OBJECTIVE: We reviewed available evidence on the glucose lowering and anti-atherogenic effects of IBT. RESULTS: In addition to their glucose-lowering and weight-neutral or weight-reducing actions, IBT decrease systolic blood pressure and improve fasting and postprandial lipid parameters by reducing total-cholesterol, low-density lipoprotein-cholesterol and triglycerides concentrations, and increasing high-density lipoprotein-cholesterol values. Reduced high-sensitivity C-reactive protein levels and improved endothelial dysfunction have been reported too. CONCLUSIONS: IBT have several beneficial effects on cardiovascular risk factors and, for this reason, it has been recently suggested to extend the use of these drugs in diabetic patients with cardiovascular complications. Yet, the long-term effects of IBT on subclinical or clinical atherosclerosis remain to be established by future studies.

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Expert Opinion

Glucose lowering and anti-atherogenic effects of incretin-based therapies: GLP-1 analogues and DPP-4-inhibitors

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Background: Type 2 diabetes is a chronic, progressive disease with a multi-faceted pathophysiology. Beyond the known defects of insulin resistance and β-cell insufficiency, derangement of incretin hormones normally produced from the gut wall in response to food intake play an important role. In recent years, the 'incretin-based' therapies (IBTs) have been developed to address hyperglycemia through either mimicking the action of the endogenous incretin glucagon-like polypeptide (GLP-1) (GLP-1 receptor agonists) or by inhibiting the activity of the enzyme that degrades GLP-1 (the dipeptyl peptidase-4 inhibitors). *Objective*: We reviewed available evidence on the glucose lowering and anti-atherogenic effects of IBT. *Results*: In addition to their glucose-lowering and weight-neutral or weight-reducing actions, IBT decrease systolic blood pressure and improve fasting and postprandial lipid parameters by reducing total-cholesterol, low-density lipoprotein-cholesterol and triglycerides concentrations, and increasing high-density lipoprotein-cholesterol values. Reduced high-sensitivity C-reactive protein levels and improved endothelial dysfunction have been reported too. *Conclusions*: IBT have several beneficial effects on cardiovascular risk factors and, for this reason, it has been recently suggested to extend the use of these drugs in diabetic patients with cardiovascular complications. Yet, the long-term effects of IBT on subclinical or clinical atherosclerosis remain to be established by future studies.

Keywords: cardiovascular risk, diabetes, DPP-4 inhibitors, GLP-1 analogues

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1. Introduction

Type 2 diabetes (T2D) is a chronic disease characterized by insulin resistance, a steady impairment in glucose-induced insulin secretion caused by a progressive decrease in β-cell function and inappropriately regulated glucagon secretion. These pathophysiologic defects result in persistent hyperglycemia and an increased risk of both microvascular and cardiovascular complications. Traditional treatments for T2D have used oral agents in a stepwise manner, followed by insulin therapy. Unfortunately, this approach does not address the progressive decline in β-cell function and is often associated with undesirable weight gain. In the past few years, new drugs that act by modulating the gut-based incretin system of hormones have been introduced for the management of hyperglycemia in T2D. These medications, collectively known as incretin-based therapies (IBTs), act by either mimicing the actions of glucagon-like polypeptide-1 (GLP-1) or by inhibiting its enzymatic

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Table 1. Characteristics of the incretin hormones GLP-1 and GIP.

GLP-1: secreted by 'L' cells in the ileum and colon
GIP: secreted by 'K' cells in the duodenum
Stimulation of glucose-dependent insulin release from the pancreas
Suppression of glucose output from the liver by glucose-dependent inhibition of glucagons secretion (GLP-1 only)
Enhanced β-cell proliferation and survival in animal models and human islet cell lines
Retardation of gastric emptying leading to early satiety
Inactivation by dipeptidyl peptidase-4 enzyme and elimination by the kidneys
Central suppression of appetite (GLP-1 only)
Reduction of fasting glucose (GLP-1 only)

GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

degradation, thus, prolonging its action. These novel agents offer the potential of reducing body weight or preventing weight gain while lowering glucose levels. Although promising, the durability of these effects and their long-term clinical benefits needs to be further elucidated. The impact of incretin-based treatments on atherosclerotic risk factors (such as blood pressure and plasma lipids) is also under investigation. Substantial evidence demonstrates that the GLP-1 receptor agonists and dipeptyl peptidase-4 (DPP-4) inhibitors produce modest reductions in systolic blood pressure and, in some cases, diastolic blood pressure. Reductions in the triglyceride level and significant improvements in total, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol have also been observed. These effects on cardiovascular risk factors are exciting potential beneficial features of IBT. The glucose-lowering and potential anti-atherogenic actions of these medications are the subject of this review article.

2. The 'incretin' concept

Incretins are hormones produced by the gastrointestinal tract in response to oral food ingestion. They help to maintain glucose homeostasis through their coordinated effects on islet α and β cells, thereby, inhibiting glucagon output and stimulating insulin secretion in a glucose-dependent manner [1]. GLP-1, the predominant incretin hormone, is produced by the L cells of the ileum, while glucose-dependent insulinotropic polypeptide (GIP) is produced by the K cells in the jejunum. In addition to their actions on endocrine pancreatic function, both GLP-1 and GIP appear to have local and CNS effects that slow gastric emptying and decrease appetite (**Table 1**). The 'incretin effect' is diminished or lost over time in people with T2D (**Figure 1**). Although GLP-1 has marked benefits in patients with T2D, native GLP-1 administration as a treatment strategy is severely limited by a short half-life *in vivo* due to inactivation by DPP-4 and the impracticality of continuous infusion. Thus, pharmacologic strategies have evolved to overcome these limitations, either directly by modifying native GLP-1 to make it resistant to the effects of DPP-4 or indirectly by inhibiting the action of DPP-4. Therefore, new treatments for T2D have been introduced recently that utilize the natural glucoregulatory effects of incretin hormones [2]. These 'incretin enhancers' are pharmacologic agents that explore a physiologic approach to the management of T2D while limiting some of the undesirable side effects such as hypoglycemia and weight gain [3,4]. They lower hemoglobin A1c (A1c), body weight and postprandial glucose excursions. Animal studies have demonstrated improvements in β-cell function *in vivo* [5].

In April 2005, the FDA approved the first incretin mimetic, exenatide, a GLP-1 receptor analogue resistant to DPP-4 degradation, as adjunctive therapy for patients with T2D. Because the GLP-1 analogues (also known as 'GLP-1 agonists' or 'mimetics'), require injection, considerable effort has been devoted to creating an oral agent targeting the incretin pathway. Inhibition of DPP-4 extends the half-life of native incretins, thereby, prolonging their effects. In October 2006, the FDA approved the first oral incretin enhancer, sitagliptin, a selective DPP-4-inhibitor, for use as monotherapy or in combination with metformin or thiazolidinedione. Additional incretin-based agents are also in late-stage development.

Exenatide mimics the actions of endogenous GLP-1 when given subcutaneously by injection, while sitagliptin and vildagliptin are agents that inhibit the enzyme DPP-4 responsible for degradation of GLP-1 and other incretins. IBT is used adjunctively in patients with T2D who fail to achieve glucose targets with oral agents. Sitagliptin and vildagliptin can also be used as monotherapy in patients T2D uncontrolled by diet. The latter medication has been approved in the EU but not in all other countries, such as the US. Once-weekly exenatide and once-daily liraglutide are other mimetics in development. Recent evidence appears to suggest that the salutary effects of IBT extend beyond glucose metabolism; thus, a stabilization of body weight and beneficial actions on lipids and blood pressure may exert a combined anti-atherogenic profile. These and other potential actions are summarized in **Table 2** and discussed in the following sections.

3. Effects on glucose metabolism

A wealth of data has been accumulated on the use of incretin mimetics and DPP-4 inhibitors in the treatment of T2D. Their actions predominantly target postprandial hyperglycemia. A critical review of Phase III clinical trials of exenatide, sitagliptin and vildagliptin [6] showed that the use of exenatide was associated with reduction in A1c levels of ~ 0.8% compared with baseline, while sitagliptin or vildagliptin lowered average A1c by 0.7%. Treatment-related hypoglycemia was generally mild, occurring mainly in combination with sulfonylureas (SUs). Exenatide treatment leads to a weight loss of around 2 kg at 30 weeks, whereas sitagliptin and vildagliptin

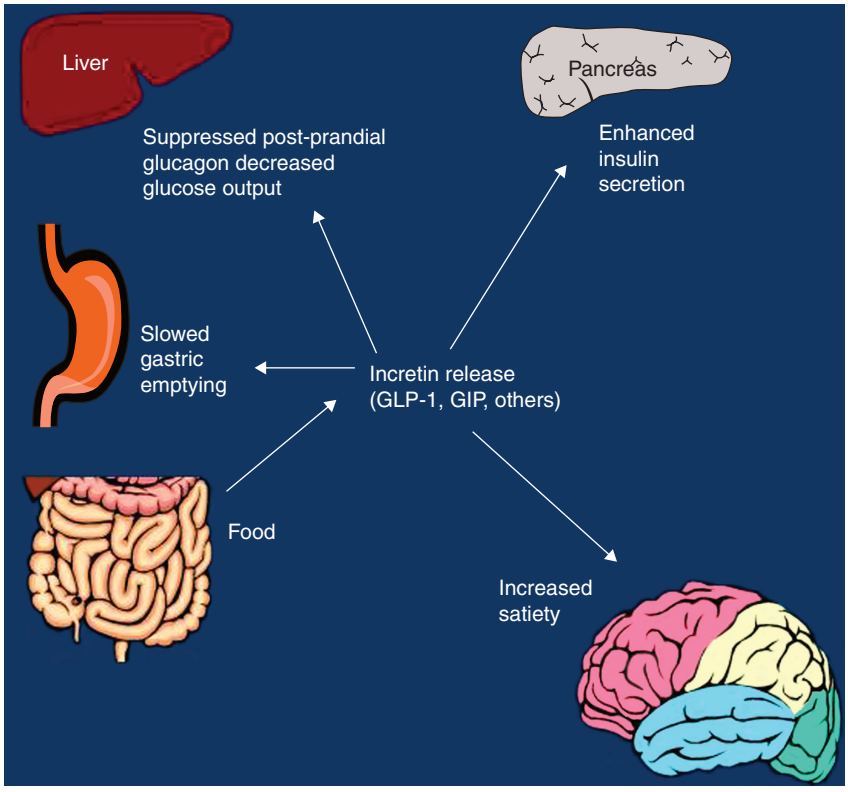

Figure 1. The incretin effect: various actions of the incretin hormones (GLP-1 and other gut hormones) released by the gastrointestinal tract in response to food ingestion. This ability is lost in type 2 diabetes.
GIP: Glucose-dependent insulinotropic polypeptide; GLP-1: Glucagon-like peptide-1.

Table 2. Potential cardiovascular benefits of therapy with incretin mimetics and enhancers (as modified from [33]).

Reduced fasting/postprandial hyperglycemia and glycoslylated hemoglobin
Improved fasting lipid parameters: reduced total- and LDL-cholesterol, triglycerides and increased HDL-cholesterol
Improved postprandial dyslipidemia
Reduced high-sensitivity C-reactive protein
Lowered systolic and diastolic blood pressure
Improved endothelial dysfunction in type 2 diabetic patients with established coronary heart disease
Improved left ventricular function in acute myocardial infarction

HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

have neutral effect on weight. About 5 – 10% of patients have adverse effects of abdominal fullness, nausea and vomiting. Dose-dependent nausea dissipates over time and is attenuated by slow titration during initiation of therapy. Sitagliptin and vildagliptin are generally well tolerated. In short, exenatide, sitagliptin and vildagliptin are useful as add-on agents for T2D that is suboptimally controlled with oral agents, particularly when there is concern about weight gain and hypoglycemia, or when postprandial hyperglycemia is predominant.

The higher the initial A1c, the more pronounced is the glucose-lowering effect of IBT. In twice-daily doses of 5 or 10 µg for 30 weeks, exenatide lowered the A1c by 1.7% in the group with a baseline A1c of 9.0% or greater, compared with 0.7% for those with a baseline A1c < 9% [7]. Interestingly, the difference was sustained with reductions of 2.0 and 0.8%, respectively, at 82 weeks. The addition of liraglutide to metformin, glimepiride, or both, for 26 weeks resulted in a greater glucose reduction with increasing A1c [8]. Patients in the upper quartile (mean baseline A1c 9.5 – 9.8%) experienced a reduction in the A1c of 1.3 – 1.8% compared with 0.5 – 0.9% for those in the lowest quartile (mean baseline A1c 7.2 – 7.3%). The challenges and feasibilities of replacing SU with IBT in patients with T2D have been addressed as well [9]. SUs can cause weight gain and increase the risk of hypoglycemia. They are thought to be associated with accelerated β-cell apoptosis, suggesting that they may actually promote the progressive decrease in β-cell mass and the need for insulin replacement. In contrast, the β-cell-preserving properties of IBT potentiate glucose-stimulated insulin secretion in T2D. The insulinotropic effects of IBT are glucose-dependent, minimizing the risk of hypoglycemia.

Administration of insulin in T2D can roughly mimic physiologic insulin secretion when used in a basal-bolus fashion. However, it does not address the underlying pathophysiology, and hypoglycemia is a potential barrier to treatment adherence and glycemic control. Weight gain can exacerbate hyperglycemia or insulin resistance. The potential of IBT for limiting weight gain while controlling glucose is in contrast to insulin [10]. In a 52-week comparison study, the addition of exenatide lowered fasting glucose and A1c (mean, -1.04%) similar to twice daily biphasic aspart insulin when added to a stable regimen of metformin/SU [11] while achieving a greater reduction in postprandial glucose and a weight loss of 5.4 kg. It follows that when oral agents have failed to maintain adequate glycemic control, IBT may be particularly well suited to the treatment of T2D patients who are overweight or obese with primarily post-meal glucose peaks. Exenatide therapy has been proposed as an alternative to insulin in patients with treatment failure with either metformin monotherapy or metformin–SU combination [10]. The exact place of IBT plus available oral antidiabetic agent treatment remains an area of ongoing study [12,13].

Liraglutide is a new GLP-1 agonist that shares considerable amino-acid homology with human GLP-1. Structural modifications, primarily the addition of a palmitate side chain, allow for greater self-association, albumin-binding to albumin, prolonged absorption and resistance to inactivation by the enzyme DPP-4. A 26-week, double-blind trial demonstrated the noninferiority of liraglutide compared to glimepiride in a cohort of overweight patients with T2D inadequately controlled with metformin monotherapy [14]. Other studies have demonstrated the beneficial effects of liraglutide on weight and body composition [15,16].

The family of oral DPP-4 inhibitors has actions on postprandial as well as fasting glucose levels. Sitagliptin is approved as monotherapy or as adjunct to metformin and SUs in the treatment of T2D, lowering A1c by a mean of -0.74% compared with placebo in a 24-week monotherapy trial without causing significant nausea or vomiting [17]. A similar but more modest effect from baseline was observed with the addition of sitagliptin to pioglitazone over a 24 week period [18]. Vildagliptin has also shown efficacy as monotherapy in clinical studies [19,20]. In drug-naive patients, vildagliptin 50 mg twice daily decreased the A1c by 1.3%, similar to rosiglitazone 8 mg daily. In patients with a baseline mean A1C of 10%, the reductions were 1.8 and 1.9%, respectively [21]. Alogliptin, still in development, has yielded similar results in patients who were inadequately controlled with lifestyle changes [22].

A recent meta-analysis of randomized controlled trials [13] showed that IBT with GLP-1 analogues or DPP-4 inhibitors in adults with T2D is effective in improving glycemia, with greater reductions in postprandial glycemia and favorable (GLP-1 analogues) or neutral (DPP-4 inhibitors) effects on weight. Regarding adverse events, glucagon-like peptide 1 analogues were associated with gastrointestinal adverse effects, while DPP-4 inhibitors had a slightly increased risk of infection (nasopharyngitis and urinary tract infection) and headache. Further, in the few available trials, incretin-based medications were found to be not inferior compared with non–incretin-based pharmacologic therapies, including insulin glargine or biphasic aspart, glimepiride, metformin, glipizide or thiazolidinediones, with the exception of metformin being superior to vildagliptin [13]. Additional trials comparing IBTs with existing therapies are also ongoing.

4. Effects on body weight

Infusions of GLP-1 reduce gastric emptying, increase satiety and mitigate hunger in clinical studies in both healthy volunteers and patients with T2D [23]. IBT has glucose-lowering actions that are associated with lack of weight gain and even weight loss. GLP-1 agonists have the potential to induce significant weight reduction concurrently with improved glycemic control, while DPP-4 inhibitors exhibit a weight-neutral profile [13]. The weight is lost from visceral fat, is mediated by gastrointestinal and CNS effects, and appears to be durable as long as therapy is continued. The actual amount of weight change, however, is variable; some individuals lose impressive amounts of weight, while others lose little or none at all. Although nausea and vomiting can occur in a subset of patients with GLP-1 agonist therapy, the weight loss is not thought to be directly attributable to these side effects. No difference in the degrees of weight loss has been observed in patients who experience gastrointestinal symptoms compared to those who do not. Some of the weight-reducing properties of IBT have been alluded to in the preceding section.

A succession of three studies evaluated the addition of exenatide 10 μg twice daily to SU, metformin or a combination of SU–metformin therapy. Weight loss ranged from a mean -1.6 to -2.8 kg over a 30-week period, and A1c levels were lowered from a mean -0.78 to -0.86% [24-26]. The weight loss with exenatide was gradual, dose-dependent and without an apparent plateau. Similar results have accrued from combination studies of exenatide to thiazolidinediones [27]. Extension studies have suggested continued weight loss in a subset of these patients. Interestingly, trials with a longer-acting preparation of exenatide (exenatide LAR) administered once weekly have demonstrated a different dose response for the glucose-lowering properties compared with the effect on body weight [28]. It appears that higher doses are required to obtain a robust and sustained reduction in weight. By 15 weeks of therapy, there was a 3.8-kg reduction in body weight in subjects treated with the highest dose.

The LEAD (Liraglutide Effect and Action in Diabetes) program represents a large series of studies undertaken in ~ 4200 patients to characterize the effect of liraglutide over the spectrum of T2D. Studies were performed with liraglutide as monotherapy, in combination with metformin, in combination with an SU, in combination with metformin and a thiazolidinedione, and in combination with metformin plus an SU [14,29,30]. A1c reductions were seen in each of these

clinical situations. A significant reduction in body weight was also observed in all arms except for the combination with SU. The magnitude of the weight loss was modest – ~ 2 – 3 kg over a 26-week period – but it appeared to be sustained over the duration of the trials (52 weeks) [31]. The greatest weight reduction occurred in those with the highest body mass index. A1c lowering was generally independent of the weight loss, except in individuals treated with metformin and liraglutide, in whom there was a correlation between greater A1c improvement and the greatest decrease in body weight. Both visceral and subcutaneous adipose tissue mass decreased with the weight loss along with amelioration in hepatic steatosis and reduction in waist circumference. An interesting reduction in systolic blood pressure of up to 6 mmHg was observed in the liraglutide-treated individuals that did not appear to be related to the weight loss [32].

5. Effects on blood pressure

Beyond the positive effects on glucose metabolism and body weight, the incretin enhancers seem to have beneficial effects on blood pressure and blood lipids that may contribute to reduced cardiovascular risk [33]. In general, modest reductions in blood pressure are observed with both GLP-1 receptor agonists and DPP-4 inhibitors. Although modest, such reductions may be of significant clinical significance in patients with T2D. Note that the National High Blood Pressure Education Program Coordinating Committee in the latest report on prevention, detection, evaluation and treatment of high blood pressure has stated that each increment of 20/10 mmHg above 115/75 mmHg doubles the risk of cardiovascular disease [34].

In a retrospective study, therapy with exenatide (5 µg twice daily for 26 weeks) in 38 obese patients not controlled with oral hypoglycemic agents and insulin led to a reduction in the systolic blood pressure (-9.2 mmHg, $p = 0.02$) [35]. Similar findings were obtained by another study that examined the long-term effects of exenatide (5 – 10 µg twice daily for 82 weeks) in overweight metformin-treated individuals; the reduction was found in both diastolic and systolic blood pressure (-4.1 and -6.3 mmHg, respectively, $p < 0.05$ for both) [36]. Other studies have investigated the effects of liraglutide on blood pressure. In a double-blind placebo-controlled study, liraglutide as monotherapy at different doses in 163 diabetic subjects for 14 weeks was able to significantly improve systolic blood pressure (up to 7.9 mmHg with the maximum dose of 1.9 mg daily); in addition, in relation to placebo, the mean diastolic blood pressure decreased significantly by 2 – 3 mmHg with all liraglutide doses [36]. The LEAD studies have further shown the beneficial effects of 26 weeks of therapy with liraglutide on blood pressure levels [37]. It should be also noted that, in general, the reductions in blood pressure seen with exenatide and liraglutide administration were not due to weight loss. Finally, sitagliptin significantly reduced blood pressure in a pilot study of 19 non-diabetic subjects with mild to moderate hypertension (9 on monotherapy and 10 on combination antihypertensive therapy), randomized to sitagliptin 50 or 100 mg or placebo twice daily for 5 days [38].

6. Effects on lipid profile

Several studies have investigated the impact of therapy of incretin enhancers on the lipid profile in patients with T2DM. Regarding DPP-4 inhibitors, sitagliptin has been found beneficial as both monotherapy and as combination therapy. Administered at doses of 5, 12.5, 25 or 50 mg twice daily for 12 weeks in subjects who were either drug-naive or on oral monotherapy (except a thiazolidinedione) [39], sitagliptin at doses greater than 5 mg reduced triglyceride levels by 9 – 14% and increased HDL-cholesterol concentrations by 4% compared to placebo ($p < 0.05$ for both).

Other authors have studied the effects of sitagliptin on plasma lipids in combination with metformin, pioglitazone, glimepiride and glipizide. When added to pre-existing metformin therapy (< 1500 mg/day), sitagliptin at doses of 100 mg/day for 24 weeks resulted in a small but significant decrease in levels of total cholesterol, triglycerides and non-HDL-cholesterol, and a small but significant increase in HDL-cholesterol concentration compared with the metformin arm (**Table 3**) [40]. The study was continued for an additional 80 weeks and results of an interim analysis at 54 weeks suggest a sustained reduction in triglycerides and HDL-cholesterol levels with sitagliptin use [41]. In another study, sitagliptin added to on-going pioglitazone therapy (30 or 45 mg/day) at doses of 100 mg/day for 24 weeks led to a significant decrease in levels of plasma triglycerides, while no significant differences were noted in the other lipid parameters (**Table 3**) [18]. Finally, in an active controlled study evaluating sitagliptin 100 mg versus glipizide 5 mg day added to metformin for 52 weeks, the former resulted in a greater increase in HDL-cholesterol concentrations (3.7 versus 1.2%) [42].

Vildagliptin also improved plasma lipid parameters in patients with metformin-resistant T2D. Patients were randomized to vildagliptin (50 mg twice daily) or pioglitazone (30 mg daily) for 24 weeks [43]. Compared to pioglitazone, vildagliptin reduced total and LDL-cholesterol by 7 and 10%, respectively ($p < 0.001$ for both); by contrast, triglycerides reduced more and HDL-cholesterol increased more after pioglitazone than vildagliptin (10 versus 1%, $p = 0.004$ and 15 versus 1%, $p < 0.001$, respectively). Similar results have been observed when compared to rosiglitazone, although the reduction in triglyceride concentrations with vildagliptin was higher (14%) than in the comparison with pioglitazone [21].

Regarding the GLP-1 receptor agonists, exenatide (5 µg twice daily, for a mean of 26 weeks) led to a reduction in total cholesterol of 8.5% ($p = 0.03$) and in triglycerides of 26% ($p = 0.01$) when added in obese patients with T2D not controlled with oral hypoglycemic agents and insulin [35]; notably, in this retrospective study, no changes in plasma

Table 3. Effects of sitagliptin (100 mg/day) added to metformin (< 1500 mg/day) or pioglitazone (30 or 45 mg/day) on plasma lipids after 24 weeks [18,40].

	Sitagliptin + metformin (n = 429)	Sitagliptin + pioglitazone (n = 151)
Total-cholesterol (mg/dl)	-2.8%*	0.0%
Triglycerides (mg/dl)	-16.9%‡	-11.2%*
HDL-cholesterol (mg/dl)	2.0%*	0.2%
LDL-cholesterol (mg/dl)	-0.8%	3.3%
Non-HDL-cholesterol	-4.8%*	0.4%

*$p < 0.05$.
‡$p < 0.001$.
Data are expressed as placebo-subtracted least squares mean % change from baseline (95% CI).
HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

lipids were observed in those patients who discontinued exenatide. In addition, in overweight patients failing to achieve glycemic control with maximal doses of metformin, exenatide (5 – 10 μg twice daily for 82 weeks) significantly reduced total and LDL-cholesterol and triglyceride levels, with a concomitant increase in HDL-cholesterol concentration. These improvements in plasma lipids were independent of weight loss [36].

Liraglutide also significantly improved triglyceride concentrations in a 14-week study performed in patients inadequately controlled on oral antihyperglycemic monotherapy [29]: triglycerides significantly decreased by 19 and 22% with doses of liraglutide of 0.65 and 1.9 mg versus placebo ($p = 0.0304$ and 0.0110, respectively). Similarly, in another study investigating the addition of exenatide or liraglutide to oral antihyperglycemic therapy, triglyceride concentrations improved more in patients treated with liraglutide than exenatide [44].

Other authors have reported the effects of incretins enhancers on postprandial lipemia (as reviewed in [45]). In a pilot study [46], treatment with GLP-1 was associated, postprandially, with reduced VLDL triglycerides, while LDL- and HDL-cholesterol concentrations were unchanged; notably, GLP-1 increased LDL particle diameter as compared to the control group. Similarly, postprandial triglycerides were reduced in another study investigating the effects of acute GLP-1 administration in healthy volunteers [47]. Matikainen *et al.* [48] investigated in a randomized, double-blind, placebo-controlled study the effect of vildagliptin (50 mg twice daily for 4 weeks) on postprandial lipemia in T2D; vildagliptin reduced postprandial levels of total triglycerides and those contained in triglyceride-rich lipoproteins.

7. Conclusion

The incretin concept, as it is currently understood, dates back to early observations that ingested glucose results in a considerably larger and more sustained insulin response than glucose administered intravenously. Impairments in the incretin response in patients with T2D may contribute to dysregulation of insulin and glucagon secretions, particularly during the postprandial period, thus, leading to hyperglycemia. The recent introduction in the market of the new antidiabetic drugs modulating the incretin system, such as the GLP-1 receptor agonists and the DPP-4 inhibitors, may open new horizons in the management of T2D.

In addition to their glucose-lowering and weight-neutral or weight-reducing actions, substantial evidence demonstrates that the GLP-1 receptor agonists and DPP-4 inhibitors produce decreases in systolic blood pressure and, in some cases, diastolic blood pressure. Furthermore, IBT has been shown to improve fasting and postprandial lipid parameters by reducing total cholesterol, LDL-cholesterol and triglycerides concentrations, and increasing HDL-cholesterol values. Improved endothelial dysfunction in T2D patients with established coronary heart disease have been reported with GLP-1 [49] and reduced high-sensitivity C-reactive protein levels with exenatide administration was found in subjects with T2D [50]. Due to these beneficial actions on cardiovascular risk factors, it has been recently suggested using these drugs in diabetic patients with cardiovascular complications (as reviewed in [51]). Yet, the long-term effects of therapies with GLP-1 receptor agonists and DPP-4 inhibitors on subclinical (e.g., increased carotid intima-media thickness) or clinical (e.g., cardiovascular morbidity and mortality) atherosclerosis remain to be established by future studies.

8. Expert opinion

The recent introduction in the market of the new antidiabetic drugs modulating the incretin system has opened new horizons in the management of T2D. The incretin concept dates back to early observations that ingested glucose results in a considerably larger and more sustained insulin response than glucose administered intravenously. Two incretins have been identified within the gastrointestinal tract with the property of stimulating insulin release: GIP and GLP-1. Impairments in the incretin response may contribute to dysregulation of insulin and glucagon secretion, particularly during the postprandial period, leading to hyperglycemia.

Although GLP-1 given experimentally has marked benefits in patients with T2D, native GLP-1 administration, as a treatment strategy, is severely limited by a short half-life *in vivo* due to inactivation by DPP-4 and the impracticality of continuous infusion. Thus, pharmacologic strategies have evolved to overcome these limitations, either directly by modifying native GLP-1 to make it resistant to the effects of DPP-4 (GLP-1 mimetics and analogues) or indirectly (by inhibiting the action of DPP-4).

A recent meta-analysis of randomized controlled trials showed that IBT with GLP-1 analogues or DPP-4 inhibitors in adults with T2D are effective in improving glycemia, with greater

reductions in postprandial glycemia and favorable (GLP-1 analogues) or neutral (DPP-4 inhibitors) effects on weight. Regarding adverse events, glucagon-like peptide 1 analogues were associated with gastrointestinal adverse effects, while DPP-4 inhibitors had a slightly increased risk of infection (nasopharyngitis and urinary tract infection) and headache. Further, in the few available trials, incretin-based medications were found to be not inferior compared with non-incretin-based pharmacologic therapies, including insulin glargine or biphasic aspart, glimepiride, metformin, glipizide or thiazolidinediones, with the exception of metformin being superior to vildagliptin. Additional trials comparing IBTs with existing therapies are also ongoing.

The appealing aspect of these agents lies in their weight-neutral or even weight-reducing effects concurrent with their glucose-lowering actions. Preliminary data suggest that IBTs may preserve β-cell function in the long-term, thus, promising to be disease-modifying drugs. Using these agents early in the diabetic process may indeed be effective in preventing the disease or retarding its progression. The GLP-1 receptor agonists could be particularly beneficial in overweight or obese patients who have cardiovascular risk factors. In particular, there is promising evidence that IBTs have salutary effects on blood pressure and lipid profile. Through beneficial actions on the risk factors that often cluster in individuals with diabetes (obesity, hyperglycemia, hypertension and dyslipidemia), incretin-based treatments may potentially reduce cardiovascular morbidity and mortality from this devastating disease. This needs to be tested by future prospective studies and will probably become one of the 'hot topics' in diabetes and cardiovascular prevention in the next few years.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Stonehouse A, Okerson T, Kendall D, Maggs D. Emerging incretin based therapies for type 2 diabetes: incretin mimetics and DPP-4 inhibitors. Curr Diab Rev 2008;4(2):101-9
2. Drucker DJ. The biology of incretin hormones. Cell Metab 2006;3:153-65
3. Blonde L, Rosenstock J, Triplitt C. What are incretins, and how will they influence the management of type 2 diabetes? J Manag Care Pharm 2006;12(7 Suppl A):S2-12
4. Bonora E. Antidiabetic medications in overweight/obese patients with type 2 diabetes: drawbacks of current drugs and potential advantages of incretin-based treatment on body weight. Int J Clin Pract 2007;61(s154):19-28
5. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. Exendin-4 stimulates both β-cell replication and neogenesis, resulting in increased β-cell mass and improved glucose tolerance in diabetic rats. Diabetes 1999;48:2270-6
6. Mikhail N. Incretin mimetics and dipeptidyl peptidase 4 inhibitors in clinical trials for the treatment of type 2 diabetes. Expert Opin Investig Drugs 2008;17:845-53
7. Blonde L, Klein EJ, Han J, et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes Obes Metab 2006;8:436-47
8. Nauck M, Brandle M, Vaag A, et al. The once-daily human GLP-1 analog liraglutide substantially reduces HbA1c in subjects with type 2 diabetes, irrespective of HbA1c at baseline. Presented at: American Diabetes Association 68th Scientific Session; June 6-10, 2008; San Francisco, California; abstract 477-P
9. Knop FK, Holst JJ, Vilsbøll T. Replacing SUs with incretin-based therapies for type 2 diabetes mellitus: challenges and feasibility. Drugs 2008;11:497-501
10. Van Gaal LF, Gutkin SW, Nauck MA. Exploiting the antidiabetic properties of incretins to treat type 2 diabetes mellitus: glucagon-like peptide 1 receptor agonists or insulin for patients with inadequate glycemic control? Eur J Endocrinol 2008;158:773-84
11. Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 2007;50:259-67
12. Serra D, He YL, Bullock J, et al. Evaluation of pharmacokinetic and pharmacodynamic interaction between the dipeptidyl peptidase IV inhibitor vildagliptin, glyburide and pioglitazone in patients with type 2 diabetes. Int J Clin Pharmacol Ther 2008;46:349-64
13. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007;298:194-206

• **Systematic review and meta-analysis of the efficacy and safety of incretin-based therapies in T2D.**

14. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (Liraglutide Effect and Action in Diabetes)-2 Study. Diabetes Care 2009;32:84-90
15. Madsbad S, Schmitz O, Ranstam J, et al. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care 2004;27:1335-42
16. Harder H, Nielsen L, Tu DT, et al. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. Diabetes Care 2004;27:1915-21
17. Aschner P, Kipnes MS, Lunceford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 2006;29:2632-7
18. Rosenstock J, Brazg R, Andryuk PJ, et al. Efficacy and safety of the dipeptidyl

peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clin Ther 2006;28:1556-68

•• **An interesting article showing the effects of sitagliptin (in combination with pioglitazone) on plasma lipids in patients with T2D.**

19. Pi-Sunyer FX, Schweizer A, Mills D, et al. Efficacy and tolerability of vildagliptin monotherapy in drug-nave patients with type 2 diabetes. Diabetes Res Clin Pract 2007;76:132-8

20. Sunkara G, Sabo R, Wang Y, et al. Dose proportionality and the effect of food on vildagliptin, a novel dipeptidyl peptidase IV inhibitor, in healthy volunteers. J Clin Pharmacol 2007;47:1152-8

21. Rosenstock J, Baron MA, Dejager S, et al. Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomized trial. Diabetes Care 2007;30:217-23

22. Defronzo R, Fleck P, Wilson C, et al. Alogliptin monotherapy improves glycemic control in patients with type 2 diabetes. Presented at: American Diabetes Association 68th Scientific Session; June 6-10, 2008; San Francisco, California; abstract 446-P

23. Gutzwiller JP, Drewe J, Göke B, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol 1999;276:1541-4

24. Buse JB, Henry RR, Han J, et al.; Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27:2628-35

25. Defronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28:1092-100

26. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28:1083-91

27. Zinman B, Hoogwerf BJ, Duran-Garcia S, et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2007;146:477-85

28. Kim D, MacConell I, Zhuang D, et al. Effects of once-weekly dosing of a long-acting release formulation of exenatide on glucose control and body weight in subjects with type 2 diabetes. Diabetes Care 2007;30:1487-93

29. Vilsboll T, Zdravkovic M, Le-Thi T, et al. Liraglutide, a long-acting human glucagon-like peptide-1 analog, given as monotherapy significantly improves glycemic control and lowers body weight without risk of hypoglycemia in patients with type 2 diabetes. Diabetes Care 2007;30:1608-10

30. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-week, phase II, double-blind, parallel-treatment trial. Lancet 2009;373:473-81

31. Nauck M, Frid A, Hermansen K, et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32:84-90

32. Colagiuri S, Frid A, Zdravkovic M, et al. Liraglutide, a human GLP-1 analogue, reduces systolic blood pressure in subjects with type 2 diabetes. Program and abstracts of the European Association for the Study of Diabetes (EASD) 44th Annual Meeting; September 7-11, 2008; Rome, Italy; abstract 899

33. Mafong DD, Henry RR. The role of incretins in cardiovascular control. Curr Hypertens Rep 2009;11:18-22

• **A recent interesting article reviewing the role of incretins in cardiovascular control.**

34. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42:1206-52

35. Viswanathan P, Chaudhuri A, Bhatia R, et al. Exenatide therapy in obese patients with type 2 diabetes mellitus treated with insulin. Endocr Pract 2007;13:444-50

36. Ratner RE, Maggs D, Nielsen LL, et al. Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with type 2 diabetes mellitus. Diabetes Obes Metab 2006;8:419-28

37. Colagiuri S, Frid A, Zdravkovic M, et al. The once-daily human GLP-1 analog liraglutide reduces systolic blood pressure in patients with type 2 diabetes. Paper presented at: American Diabetes Association 68th Scientific Session; June 6-10, 2008; San Francisco, CA

38. Mistry GC, Maes AL, Lasseter KC, et al. Effect of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on blood pressure in nondiabetic patients with mild to moderate hypertension. J Clin Pharmacol 2008;48:592-8

39. Scott R, Wu M, Sanchez M, et al. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Pract 2007;61:171-80

40. Charbonnel B, Karasik A, Liu J, et al.; Sitagliptin Study 020 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Care 2006;29:2638-43

•• **An interesting article showing the effects of sitagliptin (in combination with metformin) on plasma lipids in patients with T2D.**

41. Karasik A, Wu M, Williams-Herman D, Meininger G. Sitagliptin added to ongoing metformin therapy provides sustained glycemic control over 54 weeks, with a low incidence of hypoglycemia and with weight loss. Diabetes 2007;56(Suppl 1):A139

42. Nauck MA, Meininger G, Sheng D, et al.; Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007;9:194-205

43. Bolli G, Dotta F, Rochotte E, et al. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes Obes Metab 2008;10:82-90

44. Blonde L, Rosenstock J, Sesti G, et al. Liraglutide: superior glycemia control vs exenatide when added to metformin and/or SU in type 2 diabetes. Paper presented at: Canadian Diabetes Association/Canadian Society of Endocrinology and Metabolism Annual Meeting; October 15-18, 2008; Montreal, Quebec, Canada

45. Eleftheriadou I, Grigoropoulou P, Katsilambros N, Tentolouris N. The effects of medications used for the management of diabetes and obesity on postprandial lipid metabolism. Curr Diabetes Rev 2008;4:340-56

- **A comprehensive review on the effects on postprandial lipid metabolism of current agents used for the management of T2D.**

46. Juntti-Berggren L, Pigon J, Karpe F, et al. The antidiabetogenic effect of GLP-1 is maintained during a 7-day treatment period and improves diabetic dyslipoproteinemia in NIDDM patients. Diabetes Care 1996;19:1200-6

47. Meier JJ, Gethmann A, Gotze O, et al. Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. Diabetologia 2006;49:452-8

48. Matikainen N, Manttari S, Schweizer A, et al. Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. Diabetologia 2006;49:2049-57

49. Nystrom T, Gutniak MK, Zhang Q, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. Am J Physiol Endocrinol Metab 2004;287:E1209-15

50. Kendall DM, Bhole D, Guan X, et al. Exenatide treatment for 82 weeks reduced C-reactive protein, HbA1C, and body weight in patients with type 2 diabetes mellitus [abstract 784]. Diabetologia 2006;49(Suppl 1):475

51. Jax T. Treatment of patients with diabetes with GLP-1 analogues or DPP-4- inhibitors: a hot topic for cardiologists? Clin Res Cardiol 2009;98:75-9

- **A recent review on the future challenges for incretin-based therapies.**

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